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EXAMINER	
BARKER, MICHAEL P	
ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,994	KAWASHIMA ET AL.	
	Examiner	Art Unit	
	MICHAEL BARKER	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 7-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 7-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 7-25 are pending in this Application.

Response to Remarks

Applicant canceled claims 2-6, thereby obviating the rejections and objections over these claims.

Applicant argues the rejection of claims 5-6 under 35 USC 112, first paragraph is moot, since these claims are now canceled. However, Applicant Notes no undue experimentation would have been required to practice the methods of new claims 21-25. Specifically, Applicant argues Test 2 on p. 17 exemplifies the inhibition of human colon cancer cells, showing the efficacy of two test compounds according to the invention as measured by T/C%. Applicant also argues pp. 19 and 20 indicate the compounds of the invention are similarly effective at treating a representative number of other types of cancers including colon cancer cells, lung cancer cells, breast cancer cells, and prostate cancer cells.

Applicant's arguments are acknowledged in relation to new claims 21-25 but do not serve to obviate or prevent a rejection of claims 21-25 under 35 USC 112, first paragraph.

Applicant argues the rejection of claims 1-3, 5, and 6 under obviousness-type double patenting should be withdrawn since, "the foregoing amendments and remarks place this application otherwise in condition for allowance." (p. 6). Since this application is not in condition for allowance, the ODP rejection will be reapplied.

Obviousness-Type Double Patenting: The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(1) Claims 21-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6, 7, 12, and 13 of copending Application No. 11/847593. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of the '593 Application discloses a genus of compounds for the treatment of an immune disease, including malignant lymphoma, a solid tumor. This genus of compounds is broader than that claimed by Applicant. The method of treating a single type of solid tumor is narrower than Applicant's claims 21-24.

Claims 2 and 3 of the '593 Application allow for a compound which is identical to Applicant's genus recited in claim 1, with the exception that R1 or R2 must be a hydroxyl group. Applicant's claim 1 specifies an alkoxy at the same position. However, claim 1 of the '593 Application seems to suggest that alkoxy and hydroxyl are interchangeable,

> both or either of R_1 and R_2 represent a hydrogen atom, a hydroxyl group, a halogen, an amino group, a C_1-C_6 alkylamino group, a C_1-C_6 alkoxy group, a C_1-C_6 alkyl group, or a cyano group;

Claim 6 of the '593 Application recites a method for immunosuppression in a animal suffering from an immune disease, including malignant lymphoma, comprising administering 2-(2-difluoromethyl-4-methoxybenzimidazol-1-yl)-4-(2,6-dimethylmorpholino)-6-morpholinopyrimidine to the animal. This compound anticipates the genus of compounds in Applicant's claim 1, from which claims 21-24 depend, while

the method of the '593 Application's claim 6 anticipates the methods of Applicant's claims 21-24.

Claim 7 of the '593 Application discloses a method according to claim 1 using two compounds which differ from Applicant's genus in that R1 or R2 is hydroxyl. Applicant specifies alkoxy in the same position. Again, claim 1 suggests the hydroxyl in claim 7 could be replaced with alkoxy.

Claim 12 of the '593 Application recites a genus of compounds for use in the treatment of a tumor in a patient. This genus of compounds overlaps significantly with Applicant's claim 1. Likewise, treating a tumor reads on claims 21-24.

Claim 13 of the '593 Application narrows claim 12 and specifies specific tumor types, including those recited in Applicant's claim 25.

(2) Claims 1 and 7-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6, 10-13, 15, 21-23, 26, 27, and 29-32 of US 7071189 in view of copending Application 11/847593. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of the '189 Patent discloses a genus of compounds overlapping with Applicant's genus of compounds recited in claim 1. The compounds of the '189 Patent recite hydroxyl where Applicant requires –OY. As discussed above, the '593 Application suggests such a substitution.

Claims 2-4, 6, 10-13, 15, 21- 23, and 26 of the '189 Patent narrow the scope of claim 1 and still encompass Applicant's genus recited in claims 1 and 7-20.

Claim 27 of the '189 Patent discloses 2-(2-difluoromethyl-4-hydroxybenzimidazol-1-yl)-4-(2,2-dimethylmorpholino)-6-morpholinopyrimidine [col. 22]; 2-(2-difluoromethyl-4-hydroxybenzimidazol-1-yl)-4,6-dimorpholino-1,3,5-triazine [col. 23]; and 2-(2-difluoromethyl-4-hydroxybenzimidazol-1-yl)-4-(2,2-dimethylmorpholino)-6-morpholino-1,3,5-triazine [col. 23]. These species would anticipate Applicant's claims 1 and 7-20 except for the fact each has hydroxyl where Applicant recites alkoxy. The '593 Application cures this discrepancy.

Claims 29-32 of the '189 Patent recite a method of treating cancer using the compounds of claim 1. These methods encompass Applicant's claims 21-25.

(3) Claims 1 and 7-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of US 7307077 in view of copending Application 11/847593. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-8 of US 7307077 describe a narrow genus of compounds which is broader than but fully encompasses Applicant's genus recited in claims 1 and 7-17, with one exception. The '077 Patent recites a hydroxyl where Applicant recites –OY. As mentioned, the '593 Application cures this deficiency.

35 USC 112, 1st paragraph: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating human colon cancer, does not reasonably provide enablement for inhibiting the growth of all cancer cells, all human tumor cells, all human tumor cells which are part of a solid tumor, in vivo, or where the human tumor cell is a human colon cancer cell, human lung cancer cell, human breast cancer cell, or human prostate cancer cell in vivo.

The following factors are considered in determining whether undue experimentation is required to practice the invention of claims 17 and 18: (1) breadth of claims; (2) nature of the invention; (3) state of prior art; (4) level of ordinary skill in the art; (5) level of predictability in the art; (6) amount of direction provided; (7) working examples; and (8) quantity of experimentation required to make or use the invention. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

As a general rule, enablement must be commensurate with the scope of claim language. MPEP 2164.08 states, "The Federal Circuit has repeatedly held that 'the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)". Similar "make and use the full scope of the invention without undue experimentation" language was repeated as recently as 2005 in *Warner-Lambert Co. v. Teva Pharmaceuticals USA Inc.*, 75 USPQ2d 1865. A

By way of background, four cases are of particular relevance to the question of enablement of a method of treating cancers broadly:

(1) In *In re Buting*, 57 CCPA 777, 418 F.2d 540, 163 USPQ 689, the claim in question was drawn to using a small genus of compounds to treat cancers,

> "The method of treating a malignant condition selected from the group consisting of leukemias, sarcomas, adenocarcinomas, lymphosarcomas, melanomas, myelomas, and ascitic tumors."

The Court concluded that human testing "limited to one compound and two types of cancer" was not "commensurate with the broad scope of utility asserted and claimed".

(2) In *Ex parte Jovanovics*, 211 USPQ 907, the claims were drawn to "the treatment of certain specified cancers in humans" by the use of a genus of exactly two compounds, the N-formyl and/or N-desmethyl derivative of leurosine. In that case, Applicant submitted "affidavits, publications, and data" for only one of the compounds, and as a result, a dependent claim drawn to the use of that species was allowed. For the other species in question, no data was presented. Rather, Applicant stated only that the other derivative would be expected to be less effective. Consequently, claims to the entire genus of two compounds were refused.

(3) In *Ex parte Busse*, et al., 1 USPQ2d 1908, the claims at issue were drawn to "A therapeutic method for reducing metastasis and neoplastic growth in a mammal" using a single species. The Court noted that such utility is no longer considered to be

'incredible', but that "the utility in question is sufficiently unusual to justify the Examiner's requirement for substantiating evidence." Note also that dependent claim 5 specified "wherein metastasis and neoplastic growth is adenocarcinoma, squamous cell carcinoma, melanoma, cell small lung or glioma." The Court noted that

> "even within the specific group recited in claim 5 some of the individual terms used actually encompass a relatively broad class of specific types of cancer, which specific types are known to respond quite differently to various modes of therapy."

(4) In *Ex parte Stevens*, 16 USPQ2d 1379 a claim at issue recited, " A method for therapeutic or prophylactic treatment of cancer in mammalian hosts". This claim was refused since there was "no actual evidence of the effectiveness of the claimed composition and process in achieving that utility."

Breadth of claims: Claim 21 encompasses inhibiting the growth of "a cancer cell". Claim 22 narrows "a cancer cell" to "human tumor cell". Claim 23 narrows "human tumor cell" to a human tumor cell which is "part of a solid human tumor". Claim 24 narrows claim 23 to in vivo situations. Finally, claim 25 specifies the "cancer cell" of claim 24 is "a human colon cancer cell, a human lung cancer cell, a human breast cancer cell, or a human prostate cancer cell." Applicant's claims read on treatment of all cancer types in humans and to treatment of those specific cancers listed in claim 25.

However, cancer is not a single disease, nor is it a cluster of closely related disorders. There are hundreds of cancers, which have in common only some loss of controlled cell growth. Cancers are highly heterogeneous at both the molecular and

clinical level, something seen especially in, for example, the cancers of the breast, brain and salivary glands.

Nature of the invention and predictability in the art: With specific reference to cancers, *Ex parte Kranz*, 19 USPQ2d 1216, 1219 notes the "general unpredictability of the field [of] …anti-cancer treatment." Furthermore, the Court in *In re Application of Hozumi* et al., 226 USPQ 353, notes the "fact that the art of cancer chemotherapy is highly unpredictable". More generally, Applicant's invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Direction or guidance: Applicant provides in vitro and correlative in vivo evidence with respect to human colon cancer. At pp. 19 and 20, Applicant states that the compounds of the invention "were also effective in vitro tests using human colon cancer cells, human lung cancer cells, human breast cancer cells or human prostate cancer cells." It is assumed Applicant intends to indicate in vitro assays were run on those cancer cells named, other than human colon cancer. However, no data was presented aside from that relating to human colon cancer.

Additionally, Applicant presents no data supporting actual treatment of a human being with colon cancer. Rather, Applicant's in vivo assay utilizes human colon cancer grown in a rat.

Human colon cancer is the only type of cancer in which the in vitro data correlates with the in vivo data. No other types of cancers are listed than those discussed above. The lack of data does not support a claim to inhibition of cancer cells, human tumor cells, solid human tumors, or solid human tumors, in vivo, broadly. Furthermore, the lack of data does not support a claim to inhibiting human colon cancer, human lung cancer, human breast cancer, or human prostate cancer. It should be noted, "inhibiting the growth" of cancer is interpreted as preventing the growth of cancer 100% of the time. No known cancer drug has been shown capable of achieving such a feat.

State of the Prior Art: Anticancer agents demonstrated to be effective in vitro and in vivo against a particular type of cancer indicate a higher likelihood of efficacy in the treatment of the same type of cancer in humans. No test is fail proof, and certain agents shown to be effective in vitro and in vivo do not work in the treatment of human beings. However, by the time specific agents have been shown to be effective in vitro and in vivo, it would seem closing the gap to treatment of human beings does not require undue experimentation.

Working Examples: Applicant has provided no working examples demonstrating treatment of cancer in a human being, as claimed.

Skill of those in the art: Many mechanisms have been proposed over the decades as methods of treating the assorted cancers generally. Cytotoxic agents could be applied directly to the tumors cells, directly killing them. Immunotherapy involves stimulating the patient's immune system to attack the cancer cells, either by immunization of the patient, in which case the patient's own immune system is trained to recognize tumor cells as targets, or by the administration of therapeutic antibodies as drugs, so that the patient's immune system is recruited to destroy tumor cells by the therapeutic antibodies.

Another approach would be to increase the amount or activity of the body's tumor suppressor genes, e.g. p53, PTEN, APC and CD95, which can for example activate DNA repair proteins, suppress the Akt/PKB signaling pathway, or initiate apoptosis of cancer cells. The angiogenesis inhibitor strategy was based on cutting off the blood supply that growing tumors need by shutting off the growth of new blood vessels by, for example, suppressing proliferation of endothelial cells or inducing apoptosis of endothelial cells.

There is also the cancer stem cell paradigm, which hypothesizes that cancer could be treated generally, either by targeting the cancer stem cells themselves, or by targeting the epithelial-to-mesenchymal transition which supposedly generates the cancer stem cells. Many of these approaches have produced anti-cancer drugs.

However, despite high hopes for success, and a plausible theory why these should work for cancers generally, none of these approaches have ever produced a drug which comes anywhere near treatment or prevention of all cancers generally.

The Court in *In re Application of Hozumi* et al., 226 USPQ 353 notes,

> "In spite of the vast expenditure of human and capital resources in recent years, no one drug has been found which is effective in treating all types of cancer. Cancer is not a simple disease, nor is it even a single disease, but a complex of a multitude of different entities, each behaving in a different way."

There are compounds that treat a modest range of cancers, but no skilled artisan has yet determined how to get a compound to be effective against cancer generally, or even a majority of cancers.

Attempts to find compounds to treat the various cancers arguably constitute the single most massive enterprise in all of pharmacology, which have not resulted in finding any treatment for tumors generally. Indeed, the existence of such a "silver bullet" is contrary to the present consensus in oncology. It is now understood that there is no "master switch" for cancers generally; cancers arise from a bewildering variety of differing mechanisms.

Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. Cancers arise from a wide variety of sources, primarily a wide variety of failures of the body's cell growth regulatory mechanisms, but also such external factors such as viruses (an estimated at least 20% are of viral origin e.g. Human papillomavirus, EBV, Hepatitis B and C, HHV-8, HTLV-1 and other retroviruses, and quite possibly Merkel cell polyomavirus, and some evidence exists showing that CMV is a causative agent in glioblastoma), exposure to chemicals

such as tobacco tars, excess alcohol consumption (which causes hepatic cirrhosis, an important cause of HCC), ionizing radiation, and unknown environment factors.

Accordingly, there is substantive reason for one skilled in the art to question the objective truth of the statement of utility or its scope. The Court in *In re Novak*, 134 USPQ 335, 337-338, states that "unless one with ordinary skill in the art would accept those allegations as obviously valid and correct, it is proper for the examiner to ask for evidence which substantiates them." No such evidence has been presented in this case. Even if Applicant's assertion that cancer in general could be treated with the claimed compounds were plausible, plausibility itself would not suffice. *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1301: "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success." Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. The skill, thus, depends on the particular cancer involved. There are some cancers where the chemotherapy skill level is high, and there are multiple successful chemotherapeutic treatments. The mechanism in these situations, however, is not necessarily the same as is alleged for Applicant's claimed compounds.

Quantity of experimentation needed: Given the fact that, historically, the development of new cancers drugs has been difficult and time-consuming, the quantity of experimentation needed is expected to be great.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." Such a conclusion is justified in this case as pertains to claims 17 and 18.

Amendments to claims 21-25 to cancel all subject matter except for "treatment of human colon cancer in a subject in need thereof" will obviate this rejection.

35 USC 112, second paragraph: The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-25 recite the limitation "said tumor cell" in reference to claim 21. There is insufficient antecedent basis for this limitation in the claim, since claim 21 recites "cancer cell" as opposed to "tumor cell".

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any questions about this Office Action may be directed toward Examiner Michael Barker at 571.272.0303. If, however, attempts to reach Mr. Barker are not successful, the Examiner's supervisor, Joseph McKane, may be reached at 571.272.0699.

/MICHAEL BARKER/
Examiner, Art Unit 1626

/Kamal A Saeed/
Primary Examiner, Art Unit 1626